REMARKS

Claims 1-3, 5, 7, 10, 11, 17-19 and 24-37 are pending in the application. Applicants are cancelling herewith Claims 1-3, 5, 7, 10, 11, 17-19 and 24-37 without prejudice to, or disclaimer of, applicants' right to file continuation applications directed to the subject matter thereof. Applicants are adding herewith new Claims 38-45. New Claims 38-45 do not add new matter. Accordingly, entry of these amendments is appropriate. Following entry of the present amendments, Claims 38-45 will be pending. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

Support for New Claims

Support for new claim 38 is found throughout the specification. The use of a sub-analgesic dosage of morphine and oxycodone for the treatment of pain is implicit in the description. For example, the specification discloses on page 6, paragraph [0019], "… wherein the method achieves an analgesic effect in the patient to which the composition is administered." Paragraph [0028] on page 9 of the specification further discloses "[a]ccording to one aspect of the invention there is provided an analgesic composition, for use in the methods of the present invention, …" Therefore, it is clear from the specification that the compositions comprising a sub-analgesic dose of morphine and a sub-analgesic dose of oxycodone are used for the treatment of pain in a patient. Paragraph [0027] on page 9 of the specification discloses "[t]he present invention relates to methods for reducing the risk associated with the administration of opioid analgesics in patients diagnosed or undiagnosed with respirator illness by administering an analgesic composition…(emphasis added)." Support for new claim 39 is found, for example, in paragraph [0065] on page 19. Support for new claims 40 and 41 is found in paragraph [0020] and in original claims 8 and 9. Support for new claims 42-45 is found in paragraphs [0021] through [0024] and original claims 11-18.

Objections to the Drawings

The Examiner has objected to the drawing because the legend is allegedly not legible. As required by the Examiner, a replacement drawing are submitted herewith. Approval of the replacement drawing is respectfully requested.

Rejections Under 35 U.S.C. § 102

The Examiner has rejected claims 1-3, 7, 17-19, 24-26, 29-33, 36 and 37 under 35 U.S.C. § 102(b) as anticipated by the publication Ross et al., Pain 2000, 84, 421-428 (Ross publication). The Examiner asserts that the Ross publication, which teaches methods of administering sub-analgesic doses of morphine and oxycodone which result in antinociceptive synergy, inherently discloses a method of reducing the risk associated with the administration of opioid analgesics. Applicants have cancelled claims 1-3, 7, 17-19, 24-26, 29-33, 36 and 37 and presented new claims 38-45 directed to a method for treating a humans with a respiratory illness for pain comprising administering a sub-analgesic dose of morphine and oxycodone. The new claims further provide that such treatment produces an analgesic effect in the human and the human experiences a reduced level of respiratory depression than associated with a dosage of morphine or oxycodone required to achieve the same analgesic effect. Applicants submit that new Claims 38-45 patentably distinguish over the Ross publication

The Ross publication discloses the administration of sub-analgesic doses of morphine and oxycodone that provide antinociceptive synergy in adult rats. The combination of sub-analgesic doses of morphine and oxycodone was found to reduce the occurrence of certain CNS side effects (but not all) associated with the administration of opioid analgesics (see for example, section 3.3.2 on page 426). Specifically, the Ross publication only found that the administration of sub-analgesic doses of morphine and oxycodone reduced the side effects associated with (1) a catatonic effect and (2) the righting reflex in rats. The Ross publication

also reports that the administration of sub-analgesic doses of morphine and oxycodone did not reduce the loss of pupil reflex. Thus, a person of ordinary skill in the art would not concluded from the Ross publication that administration of sub-analgesic doses of morphine and oxycodone will reduce all undesirable CNS side effects, and, specifically, there is no suggestion in the Ross publication that such treatment will reduced respiratory depression associated with a corresponding analgesic effect produced by analgesic dosages of either morphine or oxycodone. The Ross publication is focused on the discovery that a combination of a sub-analgesic dose of morphine and a sub-analgesic dose of oxycodone produces a synergistic analgesic efficacy when administered intracerebroventricularly (i.c.v.), intraperitoneally (i.p.) and subcutaneously compared to doses of morphine or oxycodone alone. However the Ross publication does not disclose or suggest that the administration of an analgesic composition comprising sub-analgesic doses of morphine and oxycodone may be beneficial to a sub-population of patients having a respiratory illness caused by factors unrelated to opioid-induced respiratory depression, as required in new claims 38-45.

The specification describes that patients with respiratory illnesses appear to be much more sensitive to even minimal levels of sedation. Furthermore, paragraph [0013] states "[t]his increased tendency to airway obstruction can occur out of proportion to the level of sedation that the opiates achieve." Applicants are attaching hereto the publication Catley et al., Pronounced, Episodic Oxygen Desaturation in the Postoperative Period: Its Association with Ventilatory Pattern and Analgesic Regimen, Anesthesiology, 63:20-28, 1985. This article reports the result of a study of postoperative humans in which one group was treated with intravenous morphine and a second group was treated with regional anesthesia. In the group treated with intravenous morphine, a significant number of patients experienced all five types of ventilatory disturbance; *i.e.*, central apnea, obstructive apnea, paradoxical breathing, slow

respiration and small tidal volume (See Fig. 5 of Catley et al.). Conversely, significantly fewer patients experienced incidences of ventilatory disturbance in the group treated with regional anesthesia. Ten patients receiving morphine infusions had a total of 144 episodes of pronounced oxygen desaturation (SaO2 < 80%) associated with obstructive sleep apnea. In contrast, in patients receiving regional anesthesia, oxygen saturation never decreased below 87%. Catley et al. concludes that "The strong association between apnea, paradoxic breathing, and type of analgesia (table 2) suggests that morphine can disrupt the respiratory pattern of postoperative patients as well as depress the chemical control of ventilation. Thus, Catley et al. clearly demonstrates that patients with respiratory illnesses are at significant risk of experiencing respiratory depression when treated with analgesic doses of morphine.

The Ross publication is silent about the effect of the combination of sub-analgesic doses of morphine and oxycodone on patients having any particular disorder, much less patients with respiratory illnesses, or that the combination is capable of reducing any opioid-related side effects in this patient population. Although the Ross publication discloses that analgesic combinations of sub-analgesic doses of morphine and oxycodone administered by a subcutaneous route reduces the occurrence of certain side effects in rats, the incidence of other side effects, such as the pupil reflex test, were the same in rats receiving the combination of morphine and oxycodone or doses of morphine or oxycodone alone. Importantly, the Ross publication is silent regarding the side effect of the combination of sub-analgesic doses of morphine and oxycodone on the respiratory depression in rats or any patients. The Ross publication provides no disclosure or suggestion that a combination of a sub-analgesic dose of morphine and a sub-analgesic dose of oxycodone is useful for patients with respiratory illnesses, a sub-population of patients that are very sensitive to the sedation. Therefore, new claims 38-45 are not anticipated by the Ross publication because the publication does not disclose each and

every limitation of the new claims. Accordingly, withdrawal of the rejection is respectfully requested.

Applicants also submit that the present invention is not obvious under 35 U.S.C. §103 in view of the Ross publication. Applicants submit that the present invention achieves an unexpected result compared to the cited prior art. New Claims 38-45 specifically point out and claim this unexpected result. New Claims 38-45 require that the treatment with the sub-analgesic dose of morphine and the sub-analgesic dose of oxycodone must produce an analgesic effect in the patient and the patient must experience a reduced level of respiratory depression than associated with a dosage of morphine or oxycodone required to achieve the same analgesic effect. This result is completely unexpected in view of the prior art. Since the treatment produces an analgesic effect in the patient, the person of ordinary skill in the art would expect that the side effect of respiratory depression would be equivalent to the respiratory depression associated with an analgesic dose of morphine or oxycodone. Although the cited prior art discloses that the use of sub-analgesic doses of morphine and oxycodone reduce some side effects, the prior art does not disclose that such sub-analgesic doses reduced the side effect of respiratory depression, and, particularly, reduce respiratory depression in humans with respiratory illnesses. Thus, the person of ordinary skill in the art would expect the same effect on respiratory depression when analgesia is achieved with sub-analgesic doses morphine and oxycodone as with analgesic doses morphine or oxycodone. Therefore, it is surprising and unexpected that the present invention achieves an analgesic effect using sub-analgesic doses of morphine and oxycodone, but at the same time produces a reduced level of respiratory depression than would be encountered if the patient were treated with analgesic doses of morphine or oxycodone to produce the same analgesic effect. None of the prior art discloses or suggests this result and the result is unexpected. New Claims 38-45 specifically point out and

claim this unexpected effect. Thus, it is submitted that new Claims 38-45 are not obvious in view of the cited prior art and patentably distinguish over the Ross publication.

Conclusion

Applicants believe that the foregoing is a full and complete response to the Office Action. It is submitted that new Claims 38-45 are now in condition for allowance. Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and remarks. Such action is courteously solicited. Applicants further request that the Examiner call the undersigned counsel at 404-572-2589 if allowance of the claims can be facilitated by examiner's amendment, telephone interview or otherwise.

Respectfully,

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